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AN ENANTIOSELECTIVE SYNTHESIS OF THE RESORCYLIC ACID LACTONE L-783,277 *VIA* ADDITION OF AN ACETYLIDE ANION TO A TETHERED WEINREB AMIDE†

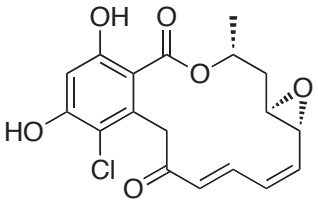
Andrew Lin, Anthony C. Willis, and Martin G. Banwell*

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia. Fax: +61-2-6125-8114
E-mail: mgb@rsc.anu.edu.au

†Dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday and in recognition of his seminal contributions to organic chemistry

Abstract – Treatment of the terminal acetylene **12**, readily obtained from the previously reported acid **10**, with LiHMDS resulted in a novel macrocyclization reaction to give the cycloalkyne **13**. Subjection of compound **13** to hydrogenation under Lindlar-type conditions afforded the *Z*-configured enone **14** that could be converted into the resorcylic acid lactone **4** upon treatment with BCl_3 in CH_2Cl_2 at –78°C.

Radicicol (**1**),[1] zearalenone (**2**)[2] and hypothemycin (**3**)[3] are iconic and long-known members of a rather large group of 14-membered and benzannulated macrolides isolated from various fungal sources and known collectively as the resorcylic acid lactones (RALs).[4] RALs display a significant range of biological properties, including a capacity for potent and selective inhibition of kinases.[4] As a result considerable effort has been devoted to the study of these compounds, including the development of syntheses,[5] and much of this has been reviewed recently.[4] In 1999 a group at Merck reported on the isolation, structural elucidation and biological evaluation of the isomeric RALs L-783,277 (**4**) and L-783,290 (**5**) both of which were obtained from a *Phoma spp*. (ATCC 74403) by bioassay guided fractionation using a kinase screen.[6] Compound **4**, a so-called *cis*-enone RAL,[7] is a potent and irreversible inhibitor of mitogen-activated protein kinase (MAPK) (IC_{50} = 4 nM) while its *trans*-isomer **5** is much less active (IC_{50} = 300 nM) against the same enzyme.[6]



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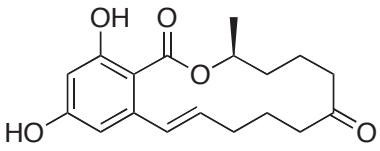

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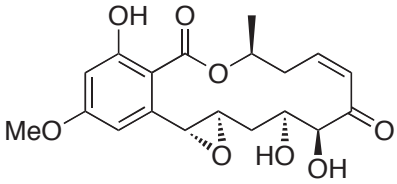

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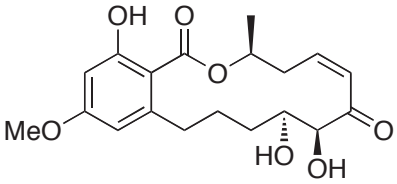

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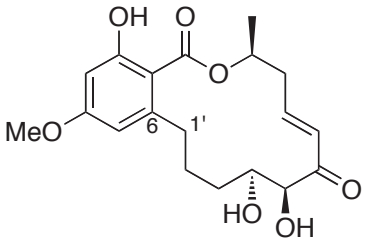
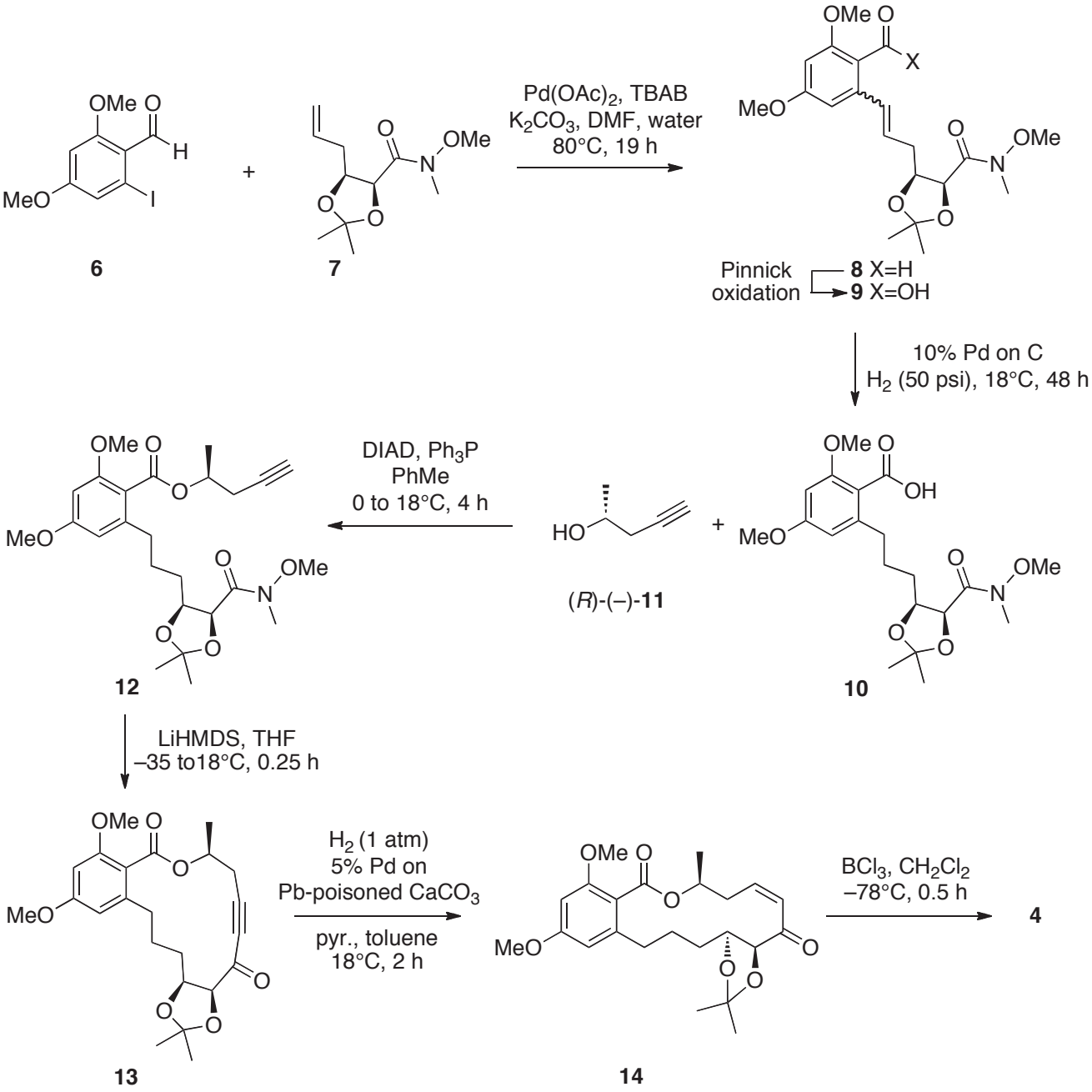


5

Recently, we reported the first total synthesis of L-783,290 (**5**) using an enzymatically-derived and enantiomerically pure *cis*-1,2-dihydrocatechol as starting material for the assembly of the south-eastern quadrant of the target.[8] The other key features of our synthesis were the use of a Heck reaction to establish the C6 to C1' linkage and a ring-closing metathesis (RCM) to form the *trans*-enone unit. Based on some of our earlier studies on the synthesis of certain non-benzannulated macrolides,[9] we attempted to effect the photo-isomerization of L-783,290 (**5**) to the more biologically active system **4**. However, all of our efforts to do so failed. Accordingly, we sought other ways to adapt our earlier work so as to establish a total synthesis of compound **4**, something that has only been achieved previously by the groups of Altmann[5i] and Winssinger.[5m] Herein we report a new total synthesis of L-783,277 (**4**) wherein the macrolide ring is established through the addition of an acetylide anion to a tethered Weinreb amide, a novel ring-forming process that does not appear to have been exploited previously in the synthesis of RALs.

The reaction sequence leading from the previously reported and readily available building blocks **6** and **7** to target **4** is shown in Scheme 1. Thus, as we have described recently,[8] compounds **6** and **7** are coupled under Heck conditions to give compound **8** as an 8:1 mixture of *E*- and *Z*-isomers in 56% combined yield. Oxidation of aldehyde **8** to the corresponding acid **9** was readily achieved in 75% yield using Pinnick's procedure[10] and the latter compound was then subjected to standard hydrogenation conditions so as to afford the previously reported[8] and saturated acid **10**. Reaction of compound **10** with the enantiomerically pure homopropargyl alcohol (*R*)-(–)-**11**, which was readily obtained through enzymatic resolution of the commercially available racemate,[11] then gave the ester **12** in 70% yield.



Scheme 1

In the pivotal step of the reaction sequence, compound **12** was treated with LiHMDS in THF at –35 to 18 °C for 0.25 h and by such means the cyclic alkyne **13** was formed in *ca*. 45% yield. Presumably, this conversion involves deprotonation of the terminal alkyne unit within substrate **12** and intramolecular addition of the resulting acetylide anion to the pendant Weinreb amide. While all the spectral data derived from compound **13** were completely consistent with the assigned structure final confirmation of this was secured through a single-crystal X-ray analysis.[12] The derived ORTEP is shown in Figure 1.

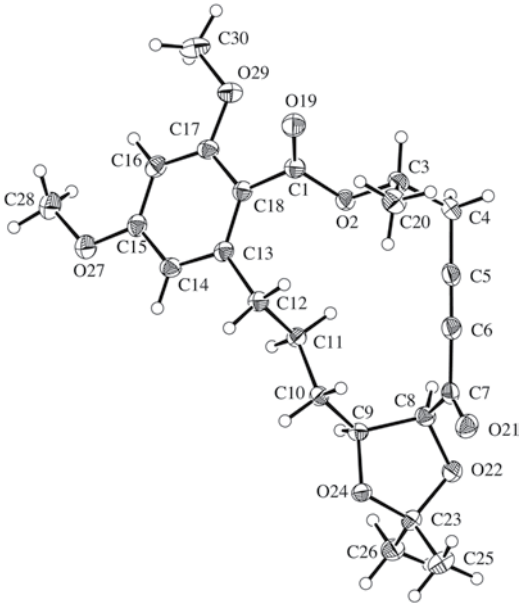


Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound **13**. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

The completion of the synthesis of target **4** involved Lindlar-type hydrogenation of alkyne **13** in the presence of pyridine and 5% Pd on lead-poisoned $CaCO_3$. The resulting *cis*-enone **14** (80%) was immediately treated with BCl_3 in CH_2Cl_2 at –78 °C for 0.5 h and L-783,277 (**4**) was thereby obtained in 50% yield. This was accompanied by *ca*. 12% of the corresponding *trans*-isomer from which it could be separated by semi-preparative HPLC. Reversing the order of the last two steps of the reaction sequence lead to a less favorable outcome. In particular, while BCl_3-mediated deprotection of compound **13** afforded the desired compound, Lindlar-type hydrogenation of this intermediate gave an inseparable mixture of compound **4**, isomer **5** and the corresponding saturated material resulting from complete reduction of the alkyne unit. The ^{13}C and ^{1}H NMR spectral data derived from the synthetic sample of compound **4** obtained by the route shown in Scheme 1 were in complete accord with the assigned structure[13] and matched those reported[6] for the natural product.

The longest linear sequence associated with the synthesis of L-783,277 described here is 16 steps from commercially available material. The Altmann synthesis is just one step longer while the Winssinger route comprises some twenty steps. The kinase inhibiting effects of compounds **4** and **5** as well as various congeners available using the chemical sequences described above will be reported in due course.

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REFERENCES AND NOTES

1. (a) P. Delmotte and J. Delmotte-Plaquée, *Nature*, 1953, **171**, 344; (b) R. N. Mirrington, E. Ritchie, C. W. Shoppee, W. C. Taylor, and S. Sternhell, *Tetrahedron Lett*., 1964, **5**, 365; (c) F. McCapra, A. I. Scott, P. Delmotte, J. Delmotte-Plaquée, and N. S. Bhacca, *Tetrahedron Lett*., 1964, **5**, 869; (d) H. G. Cutler, R. F. Arrendale, J. P. Springer, P. D. Cole, R. G. Roberts, and R. T. Hanlin, *Agric. Biol. Chem*., 1987, **51**, 3331.
2. (a) M. Stob, R. S. Baldwin, J. Tuite, F. N. Andrews, and K. G. Gillette, *Nature*, 1962, **196**, 1318; (b) W. H. Urry, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy *Tetrahedron Lett*., 1966, **7**, 3109; (c) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, 1968, **24**, 2443.
3. (a) M. S. R. Nair and S. T. Carey, *Tetrahedron Lett*., 1980, **21**, 2011; (b) M. S. R. Nair, S. T. Carey, and J. C. James, *Tetrahedron*, 1981, **37**, 2445; (c) T. Agatsuma, A. Takahashi, C. Kabuto, and S. Nozoe, *Chem. Pharm. Bull*., 1993, **41**, 373.
4. For useful reviews dealing with this class of compound, see: (a) N. Winssinger and S. Barluenga, *Chem. Commun*., 2007, 22; (b) S. Barluenga, P.-Y. Dakas, M. Boulifa, E. Moulin, and N. Winssinger, *C. R. Chim*., 2008, **11**, 1306; (c) T. Hofmann and K.-H. Altmann, *C. R. Chim*., 2008, **11**, 1318; (d) S. Bräse, A. Encinas, J. Keck, and C. F. Nising, *Chem. Rev*., 2009, **109**, 3903.
5. For representative examples of recent synthetic studies in the area, see: (a) R. M. Garbaccio, S. J. Stachel, D. K. Baeschlin, and S. J. Danishefsky, *J. Am. Chem. Soc*., 2001, **123**, 10903; (b) I. Tichkowsky and R. Lett, *Tetrahedron Lett*., 2002, **43**, 4003; (c) X. Geng and S. J. Danishefsky, *Org. Lett*., 2004, **6**, 413; (d) S. Barluenga, E. Moulin, P. Lopez, and N. Winssinger, *Chem. Eur. J*., 2005, **11**, 4935; (e) S. Barluenga, P.-Y. Dakas, Y. Ferandin, L. Meijer, and N. Winssinger, *Angew. Chem. Int. Ed*., 2006, **45**, 3951; (f) J. Lu, J. Ma, X. Xie, B. Chen, X. She, and X. Pan, *Tetrahedron: Asymmetry*, 2006, **17**, 1066; (g) N. Q. Vu, C. L. L. Chai, K. P. Lim, S. C. Chia, and A. Chen, *Tetrahedron*, 2007, **63**, 7053; (h) P.-Y. Dakas, S. Barluenga, F. Totzke, U. Zirrgiebel, and N. Winssinger, *Angew. Chem. Int. Ed*., 2007, **46**, 6899; (i) T. Hofmann and K.-H. Altmann, *Synlett*, 2008, 1500; (j) C. C. Chrovian, B. Knapp-Reed, and J. Montgomery, *Org. Lett*., 2008, **10**, 811; (k) L. J. Baird, M. S. M. Timmer, P. H. Teesdale-Spittle, and J. E. Harvey, *J. Org. Chem*., 2009, **74**, 2271; (l) F. Calo, J. Richardson, and A. G. M. Barrett, *Org. Lett*., 2009, **11**, 4910; (m) P.-Y. Dakas, R. Jogireddy, G. Valot, S. Barluenga, and N. Winssinger, *Chem. Eur. J*., 2009, **15**, 11490. For an enzymatic approach, see: (n) H. Zhou, K. Qiao, Z. Gao, M. J. Meehan, J. W.-H. Li, X. Zhao, P. C. Dorrestein, J. C. Vederas, and Y. Tang, *J. Am. Chem. Soc*., 2010, **132**, 4530.
6. (a) A. Dombrowski, R. Jenkins, S. Raghoobar, G. Bills, J. Polishook, F. Peláez, B. Burgess, A. Zhao, L. Huang, Y. Zhang, and M. Goetz, *J. Antibiot*., 1999, **52**, 1077; (b) A. Zhao, S. H. Lee, M. Mojena,

R. G. Jenkins, D. R. Patrick, H. E. Huber, M. A. Goetz, O. D. Hensens, D. L. Zink, D. Vilella, A. W. Dombrowski, R. B. Lingham, and L. Huang, *J. Antibiot*., 1999, **52**, 1086.

7. A. Schirmer, J. Kennedy, S. Murli, R. Reid, and D. V. Santi, *Proc. Nat. Acad. Sci*., 2006, **103**, 4234.
8. A. Lin, A. C. Willis, and M. G. Banwell, *Tetrahedron Lett*., 2010, **51**, 1044.
9. K. A. B. Austin, M. G. Banwell, D. T. J. Loong, A. D. Rae, and A. C. Willis, *Org. Biomol. Chem*., 2005, **3**, 1081.
10. (a) B. S. Bal, W. E. Childers Jr., and H. W. Pinnick, *Tetrahedron*, 1981, **37**, 2091; (b) M. Lang and W. Steglich, *Synthesis*, 2005, 1019.
11. The protocol used was the same as that employed for the resolution of the analogous homoallylic alcohol: (a) M. G. Banwell and D. T. J. Loong, *Org. Biomol. Chem*., 2004, **2**, 2050. Alcohol (*R*)-(–)-**11** has also been obtained in enantiomerically pure form from commercially available (*R*)-(+)-propylene oxide: (b) C. Dimitriadis, M. Gill, and M. F. Harte, *Tetrahedron: Asymmetry*, 1997, **8**, 2153.
12. *Single-crystal X-ray analysis of compound **13***: $C_{23}H_{28}O_7$, M = 416.47, T = 200 K, orthorhombic, space group $P2_12_12_1$, $Z = 4$, a = 8.6558(1), b = 8.9051(2), c = 28.2982(5) Å, V = 2181.25(7) Å^3, D_x = 1.268 g cm^{-3}, 2937 unique data ($2\theta_{max}$ = 55.8°), R = 0.038 [for 2429 reflections with $I > 2.0\sigma(I)$]; *Rw* = 0.081 (all data), S = 1.01. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC-781986). These data can be obtained free-of-charge *via* www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
13. *Selected spectral data derived from compound **4***: $[\alpha]_D$ = –15.3 (*c* 0.15, $CHCl_3$); ^{1}H NMR (800 MHz, CD_2Cl_2) δ 12.21 (s, 1H), 6.46 (ddd, J = 11.2, 3.2 and 0.8 Hz, 1H), 6.39 (d, J = 2.4 Hz, 1H), 6.36 (d, J = 2.4 Hz, 1H), 6.32 (td, J = 11.2 and 2.4 Hz 1H), 5.48 (m, 1H), 4.57 (d, J = 2.4 Hz, 1H), 3.87 (m, 1H), 3.86 (s, 3H), 3.41 (m, 1H), 3.03 (m, 1H), 2.62 (dm, J = 17.6 Hz, 1H), 2.55 (m, 1H), 1.79 (m, 1H), 1.59 (m, 2H), 1.23 (m, 1H), 1.49 (d, J = 5.6 Hz, 3H) (signals due to aliphatic hydroxyl groups not observed); ^{13}C NMR (200 MHz, CD_2Cl_2) δ 200.4, 172.2, 167.0, 164.8, 148.0, 146.7, 126.7, 109.7, 104.9, 99.4, 81.6, 74.0, 73.6, 55.9, 37.6, 37.0, 33.5, 29.4, 21.2; IR ν_{max} 3315, 2921, 2850, 1727, 1683, 1648, 1615, 1568, 1461, 1420, 1379, 1350, 1313, 1291, 1252, 1220, 1203, 1053, 1038, 1016, 902, 870, 838, 795, 748, 712 cm^{-1}; HRMS Found: $(M + Na)^+$, 387.1418. $C_{19}H_{24}O_7$ requires $(M + Na)^+$, 387.1420.